

PRINCIPLE: Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

1. Definitions:

Adverse Events (AEs) are patient reported symptoms that have started or worsened since the participant has been randomised. All AEs in IMP arms require reporting, but there are specific pre-defined symptoms that require additional follow up by the Safety Monitor. These are outlined in the PRINCIPLE protocol and Intervention Specific Appendices (ISA) for each IMP. AEs will not be collected for usual care.

Serious Adverse Events (SAEs) is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation, results in persistent or significant disability/incapacity or consists of a congenital anomaly. Other important events may also be considered SAE upon appropriate medical judgement. Hospitalisation and/or death due to COVID-19 is a primary outcome, we will collect this data using a risk-adapted approach and will not report such SAEs. **Any SAEs other than hospitalisation or death due to COVID-19 must be reported for all treatments and Usual Care.** SAEs must be reported by the person who has discovered the SAE or nominated delegate within 24 hours of becoming aware of the event.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are serious adverse reactions to the IMP that are not expected/specified in the Reference Safety Information for the IMP. Any potential SUSARs need to be reported within 7 calendar days to the relevant competent authority. This process is outlined in 'PC-CTU_SOP_TM119 5.0 Pharmacovigilance'.

Hospitalisations are defined as an admission to a hospital that requires the participant to be admitted overnight. This does not include outpatient clinics or same day discharge admissions. Hospitalisation for a pre-existing condition, including pre-planned elective procedures, which has not worsened, does not constitute an SAE, and standard supportive care for the disease under study are not SAEs and do not require SAE reporting.

This WI refers to processes specific for the PRINCIPLE trial, the 'PC-CTU_SOP_TM119 5.0 Pharmacovigilance' provides full details of the SAE and AE reporting process and timelines for reporting.

Trial Resources:

- **PRINCIPLE Protocol**
- **TMF A16.1: SAE log** (excel spreadsheet) – to log all reported SAEs.
- **Principle-safety@phc.ox.ac.uk email** account – automatic (S)AE alerts will be sent to this email account.

- **AE CRF** in OpenClinica
- **SAE CRF** in OpenClinica
- **SAE CI assessment form**
- **24 hour safety phone line (0800 9150045)**
- **Safety Follow-up Letter** sent to the GP if there is no contact with the participant.
- **OpenClinica and Sentry** databases
- **PRINCIPLE Safety Whatsapp Group** - for the Safety Monitor and trial team members to discuss any issue with (S)AE's.

2. Process:

2.1 Notification of (S)AE:

1. (S)AEs are reported in the following ways:

I. In CRFs:

AEs: Daily Diary, Call on Day 7, 14 and 28

SAEs: Daily Diary, Call on Day 7, 14 and 28, Notes Review, Hospitalisation/Death Form

- II. A member of the clinical team may be notified of an (S)AE when a participant calls the PRINCIPLE 24 hour safety telephone line.
- III. A member of the on-site trial team may be notified of an (S)AE during the day 3 call or from an unscheduled incoming call from a participant
- IV. SAEs: RSC data extracts

2. (S)AEs are monitored in the following ways:

- I. (S)AE alerts are set-up to automatically email the PRINCIPLE Safety inbox (principle-safety@phc.ox.ac.uk) whenever a potential (S)AE is inputted into OpenClinica by the patient via diaries or the trial team. The Safety Monitor or a delegated member of the trial team will monitor these automatic safety alert emails daily to review for new (S)AEs as defined in the protocol and ISA.
- II. Non-COVID hospitalisations reported in the daily diaries, Day 7/14/28 call CRF, and Note Reviews will generate an automatic email the PRINCIPLE Safety inbox (principle-safety@phc.ox.ac.uk) to be reviewed by the trial team for SAEs.

- III. For unlicensed IMPs if there has been no contact from the participant or study partner since randomisation i.e. no diary entries or telephone contact at the day 7/14/28 time points, a member of the trial team will contact the participants GP to check for any (S)AE's since starting the trial.
- IV. For (S)AE alerts via the 24 hour safety phone line the Safety Monitor will record the details of the discussion on the PRINCIPLE 24H Safety Line Log (Excel SharePoint) and if necessary report the (S)AE details in the SAE log and/or OC as described below.
- V. All (S)AE's reported from Day 3 call, incoming calls, emails or any other communication outside routine follow-up will be flagged to the Trial Manager or Safety Monitor for reporting and follow up as described below.

2.2 AE Reporting

Any new or worsening symptoms that start within the 28 day study period for participants in the IMP arms (not usual care) will be reported as an AE. Each AE will be recorded in an AE CRF form on OC. The Safety Monitor will monitor new AE CRFs and will confirm if they consider it related to COVID-19 or to the study treatment. Severity of the AE will be determined by the participant from the report in their symptom diary.

2.3 AE's requiring additional follow up:

For unlicensed IMP arms (Favipirivir and Ivermectin), there are pre-defined Moderate/Major patient-reported AEs in the ISA that require additional clinical monitoring. The windows for this additional follow up are as follows: for Favipirivir up to 5 days after starting IMP and for Ivermectin up to 14 days after starting IMP.

The Safety Monitor will review the safety alerts and contact the participants who experience these predefined AEs to advise on the appropriate clinical care, within 24 hours. Any follow-up and resolution of the AE will be recorded on the AE CRF.

All AE's will be recorded directly into OC and any additional follow up required will be tracked through OC.

2.4 SAE Reporting:

1. All overnight hospital admissions and/or deaths for any reason other than COVID-19 that start during the patient's 28 day study period will be reported as an SAE. Hospitalisation for a pre-existing condition, including elective procedures planned

prior to study entry, which has not worsened, does not constitute an SAE. SAEs are reported for all trial arms, including usual care.

2. When a new SAE occurs it must be reported within 24 hours of the site becoming aware. The SAE will be logged on the SAE log in the PRINCIPLE TMF (section A16.1) taking the next free row and the next SAE ID number. The SAE needs to be flagged immediately to the Safety Monitor for review, follow-up, and they will need to complete the SAE CRF in OpenClinica.
3. The SAE CRF will be saved as a pdf in the TMF (section A16.3.3). This will be reviewed by a CI, who will complete the CI assessment form (TM119-G_v2.0_CI_SAE_Assessment_Form) to confirm causality and expectedness. If the Safety Monitor and/or CI assessment indicate that this is a SUSAR please see 2.6 below.

2.5 Participant Follow-up for SAE's:

If any further information is outstanding for the SAE resolution, the Safety Monitor will follow up with the participant and/or their GP to enable full completion of the SAE form. If the SAE has not resolved at the 28 day time point the SAE will be reviewed again to see if resolution has occurred. If the event is considered 'resolved' or 'resolving' no further follow up is required. If not, the event must be followed up until such a time point.

If participant has withdrawn from IMP only or further calls and contact, their GP will be contacted for further details. If a patient withdraws completely from the study, including contact to the GP, the SAE will be closed as no further information will follow.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

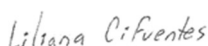
- The event resolves
- The event stabilises
- The event returns to "baseline", if a "baseline" value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

2.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any SAE that is considered definitely, probably or possibly related to the IMP (recorded as a Serious Adverse Reaction (SAR)) after the CI assessment and is not listed in the specific IMP's ISA section of the protocol or in the IMP's Investigator Brochure (therefore 'unexpected') should be considered a SUSAR. The CI or delegate completing the CI SAE Assessment Form (TM119_G) should alert the trial team to the outcome of SUSAR immediately. The trial team will process the SUSAR according to the PC-CTU_SOP_TM119 5.0 Pharmacovigilance SOP with the help of the clinical team and Chief Investigator.

2.7 Monthly Safety Audit

As part of the safety oversight a member of the PRINCIPLE trial team will conduct a safety audit of the reported (S)AE's and Safety folder in the TMF. The audit will include following up any ongoing (S)AE's. The safety audit report and actions will be discussed with the trial team and Safety Monitor during the regular safety meetings. Any actions should be completed prior to the next scheduled safety review.

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